Initial Biomarker and Clinical Findings from the CANaspire Canavan Disease Gene Therapy Trial: Exploration of Connections between NAA and Disease Severity

American Society of Cell and Gene Therapy
May 20, 2023

Florian Eichler, MD (presenting author)[1]

Amanda Nagy[1], Genevieve Laforet[2], Christine Burton[2], Kathleen M. Kirby[3], Bernard Kinane[1], Elise Townsend[1], Michael Kiefer[1], Beth Leiro[2], Rachel Williams[2], John Balser[4], Lisa Kratz[5], Adam Shaywitz[2], Annette Bley[6]

[1]Massachusetts General Hospital, Boston, MA, [2]Aspa Therapeutics, a BridgeBio Company, Palo Alto, CA, [3]Viridian, Barnstable, MA, [4]Veristat, Southborough, MA, [5]Kennedy Krieger Institute, Baltimore, MD, [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Author Disclosures and Disclaimer

Florian Eichler:

- PI of in vivo gene therapy trial in Canavan disease sponsored by Aspa Therapeutics, a subsidiary of BridgeBio Pharma
- Co-PI of ex vivo lentiviral gene therapy trial in cerebral adrenoleukodystrophy sponsored by bluebird bio
- Co-PI of in vivo gene therapy trial in GM2 sponsored by Sio Therapeutics
- Site-PI of trials in late onset GM2 sponsored by Sanofi Therapeutics and in Alexander Disease sponsored by Ionis Therapeutics
- Consultant to Autobahn, Poxel, Takeda, SwanBio Therapeutics, UpToDate and Taysha Gene Therapies
- Founder of SwanBio Therapeutics

Amanda Nagy: No disclosures

Genevieve Laforet, Chrissy Burton, Rachel Williams, Adam Shaywitz: full-time employees and stockholders of BridgeBio Pharma

Kathleen Kirby: former employee and stockholder of BridgeBio Pharma

Bernard Kinane: No disclosures

Elise Townsend: consultant to Aspa Therapeutics, a subsidiary of BridgeBio Pharma, and Biogen

Michael Kiefer: receives financial compensation as an independent contractor for ASPA Therapeutics

Beth Leiro: SME and consultant for Aspa Therapeutics, a subsidiary of BridgeBio Pharma

John Balser: consultant to Aspa Therapeutics, a subsidiary of BridgeBio Pharma

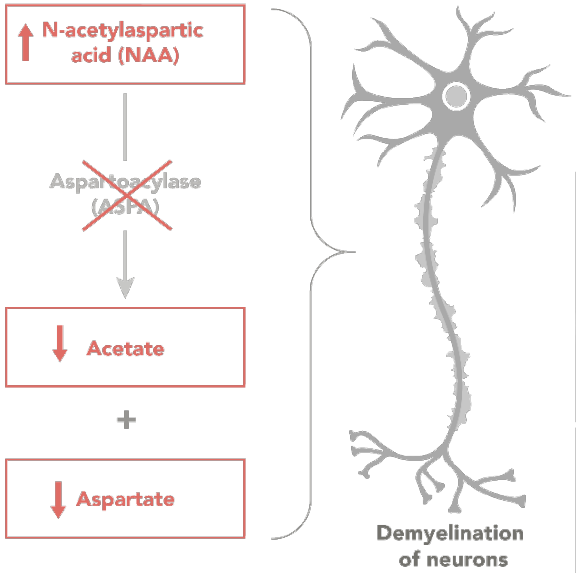
Lisa Kratz: No disclosures

Annette Bley: PI of Canavan disease natural history study CVN 101 (sponsored by Aspa Therapeutics), PI of PeriNAA-research project (sponsored by the German Government BMBF)

BBP-812 is under investigation and has not been approved by the FDA or any other regulatory authority

Canavan Disease

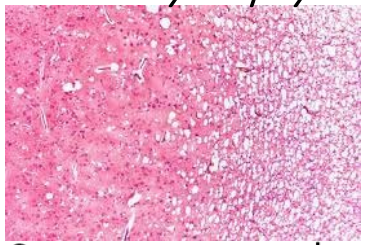
- Ultra-rare (1:100,000), autosomal recessive leukodystrophy (brain white matter disorder)
- Caused by loss-of-function mutations in *ASPA*
- Aspartoacylase enzyme deficiency leads to
  - ***NAA buildup in brain, CSF, urine***
  - Decreased acetate and aspartate production
- Results in failure to properly build and maintain CNS myelin, ***visible early in the brainstem and cerebellar peduncles***



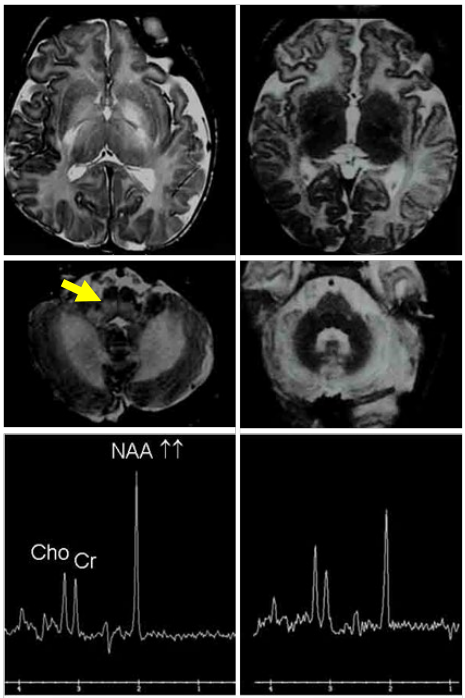
Clinical features:

- Accelerated head growth
- Poor head control
- Nystagmus, abnormal visual tracking
- Hypotonia, delayed motor development
- Seizures
- Fatal in childhood or adolescence

Spongiform leukodystrophy

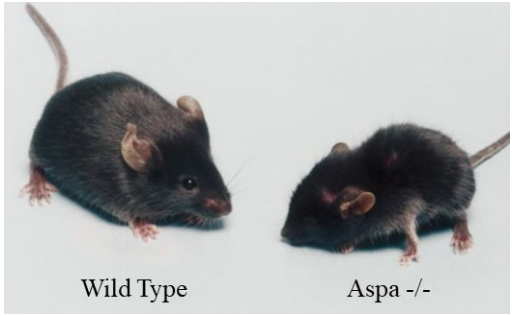


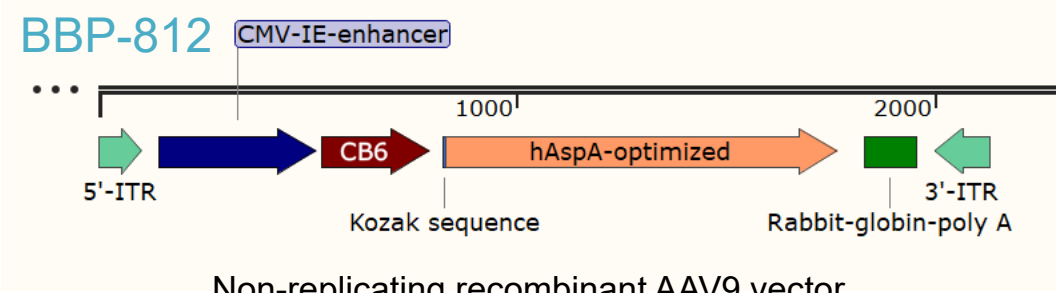
Canavan normal



Matalon R et al. GeneReviews (Internet). 1999 Sep 16, 2018 Sep 13

BBP-812: Non-clinical Evidence Supporting Systemic AAV9-*ASPA* Administration in Canavan Disease

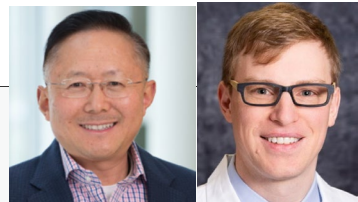




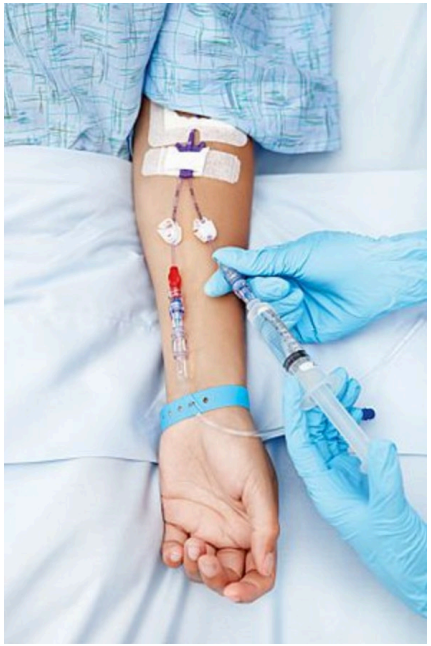
Non-replicating recombinant AAV9 vector

- *Aspa* -/- mouse model recapitulates key features of Canavan disease, including **NAA buildup**
- IV AAV9 *ASPA* gene therapy with BBP-812 led to dose-dependent improvements in NAA levels, histopathology and motor function
- Complete normalization of NAA and motor function at highest dose level

Gessler DJ et al. JCI Insight. 2017 Feb 9;2(3):e90807.

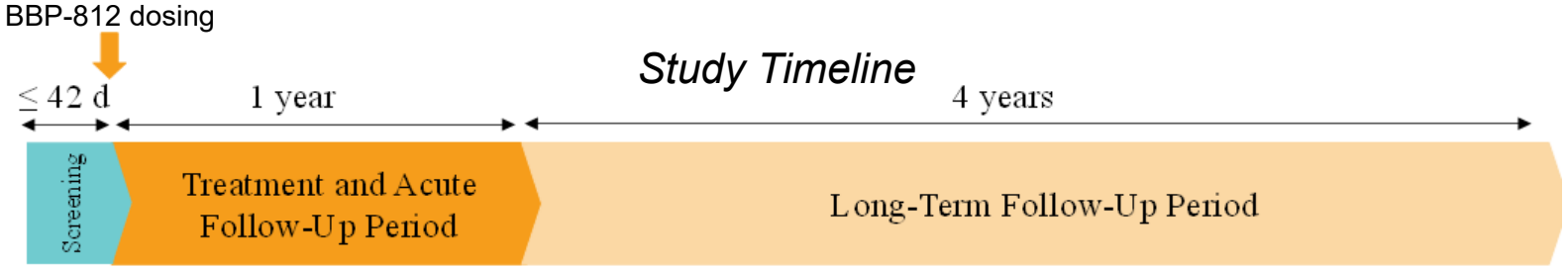


Systemic AAV9-h*ASPA* (BBP-812) Administration in Children with Canavan Disease: Study CVN-102



CANaspire
Gene Therapy Clinical Trial

CVN-102 Phase 1/2 First-in-Human Study of AAV9 Gene Therapy for Canavan Disease



- Open-label dose-finding, dose expansion trial w external control (CANinform natural hx study)
- BBP-812 dose levels: 1.32E14 vg/kg, 3.0E14 vg/kg – all participants to date rec'd low dose
- Assessments:
  - Safety and tolerability
  - NAA levels (urine, CSF, brain), motor/developmental assessments, imaging (MRI, MRS), QoL
- Eligibility:
  - Clinical, biochemical and genetic diagnosis of Canavan disease
  - Age ≤ 30 months at dosing
  - AAV9 total antibody-negative

https://clinicaltrials.gov/ct2/show/NCT04998396

CVN-101 Natural History Study

- International Canavan disease natural history study, initiated fall 2019
- Intended to provide comparator group and inform endpoint selection for CVN-102
- Eligibility: anyone with a clinical and biochemical diagnosis of Canavan disease, living or deceased
- Retrospective (all) and prospective (optional)
  - Systematic data extraction from medical records
  - Periodic motor, developmental and neurological assessments
    - Due to pandemic, motor assessments done remotely via video
    - Same assessments and raters in CVN-101 and CVN-102
- Enrollment to date: 55 participants from 14 countries

Comprehensive Array of Assessment Tools Used in CVN-101 Natural History Study

Pre-COVID Assessments	
Development/ Motor	TIMPSI Test of Infant Motor Performance Screening Items
	GMFM-88 Gross Motor Function Measure, 88 Items
	Bayley 4 Bayley Scales of Infant Development
	HINE-2 Hammersmith Infant Neurological Examination, Section 2
	CDC Developmental Milestone Checklist
Disease Severity	Canavan Disease Rating Scale (CDRS)
Impact on Family	Vineland 3 Adaptive Behavior Scales, Expanded Interview Form
	PedsQoL-FIM Pediatric Quality of Life Inventory (Family Impact Module)
	Canavan Questionnaire

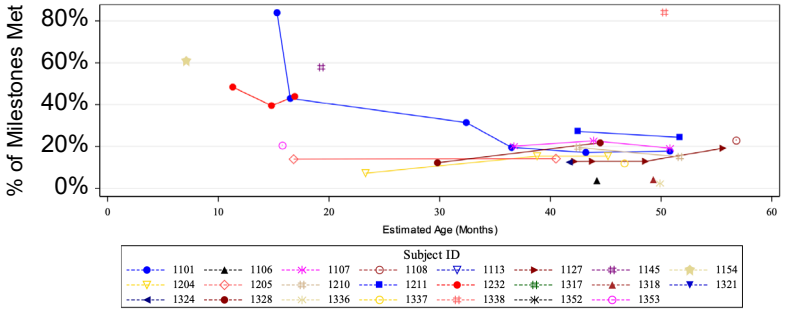
Replacements for TIMPSI, GMFM-88 and Bayley 4 for Remote/Video Administration post COVID
AIMS - Alberta Infant Motor Scale
IMP - Infant Motor Profile
Response to Sensory Stimuli Responses to auditory and visual stimuli excerpted from Bayley 4 &TIMPSI

- No validated scales for Canavan disease
- Expert clinicians and researchers guided selection of assessments
  - Parental input regarding clinical meaningfulness
- Robust training methods, same team of expert raters across natural history and gene therapy studies

Data From Ongoing CVN-101 Natural History Study Demonstrate Persistent, Impaired Motor Function

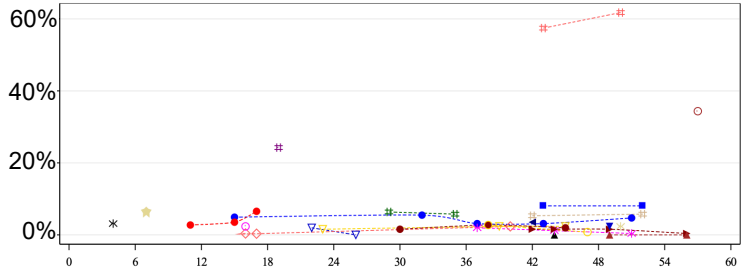
Children with Canavan Disease Function at or Below the 6-month Level

CDC Milestones Achieved (% Expected)
Retrospective + Prospective



Checklist of developmental skills across various domains that are expected to be mastered in normally developing infants and young children over the first few years of life.

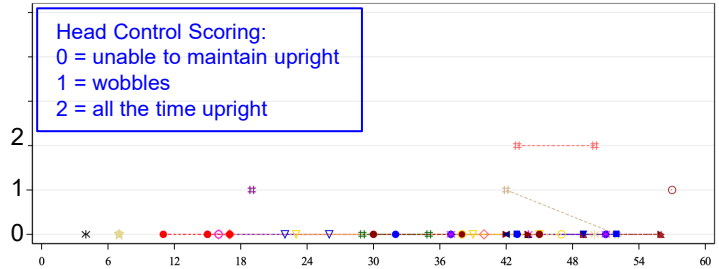
GMFM-88 – Total Score
Prospective, Rater-Assessed



Measures gross motor function in children 5 months – 16 years of age.
GMFM-88 does not have age-related norms but *typically developing children would be expected to have mastered all GMFM-88 skills by 5 yrs (total score =100%).*

HINE-2 - Head Control
Prospective, Rater-Assessed

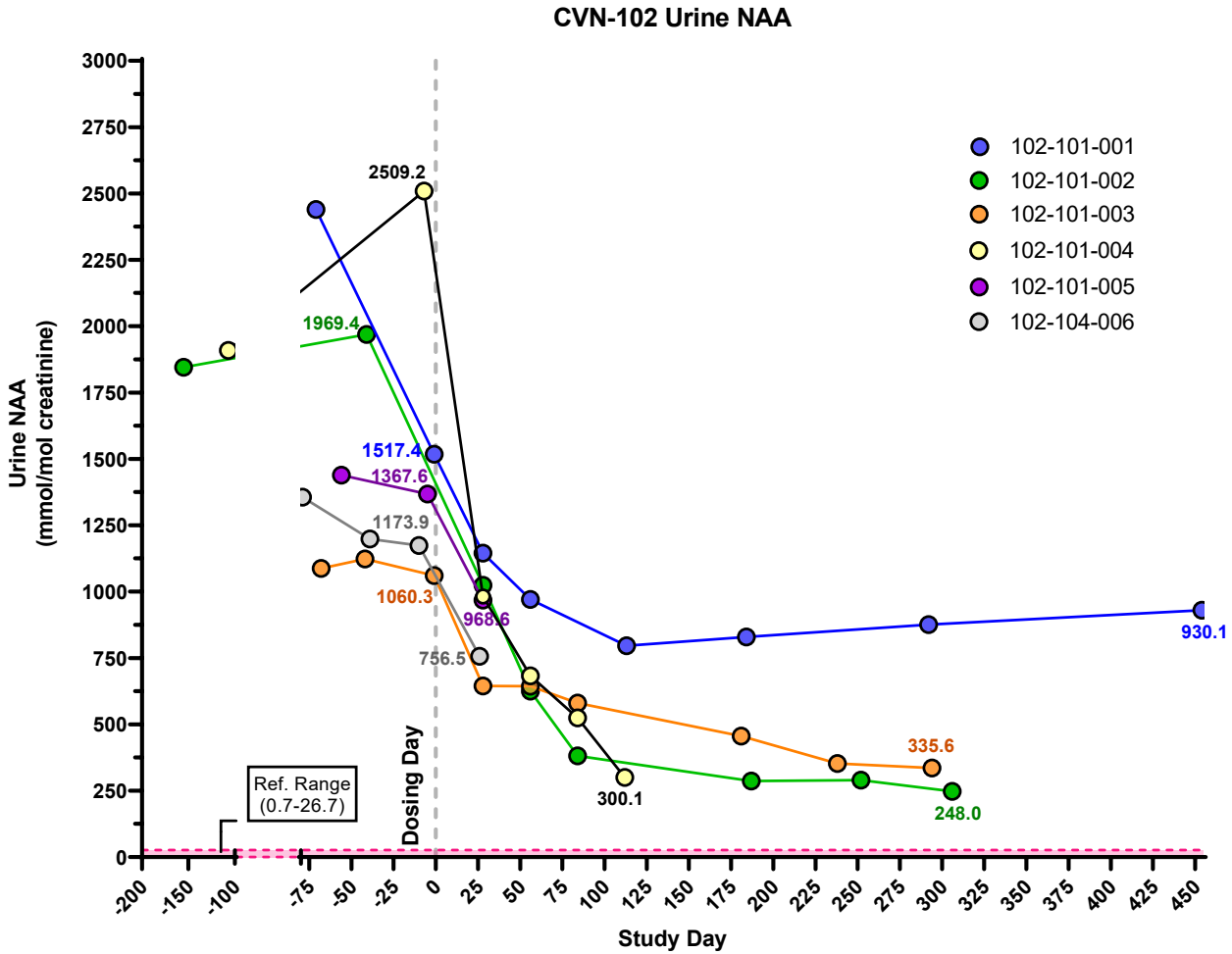
Per CDC, head control is a 4-month skill in typically developing children



Measures developmental milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) **in infants from 2 to 24 months of age.**

Aspa
a bridgebio company

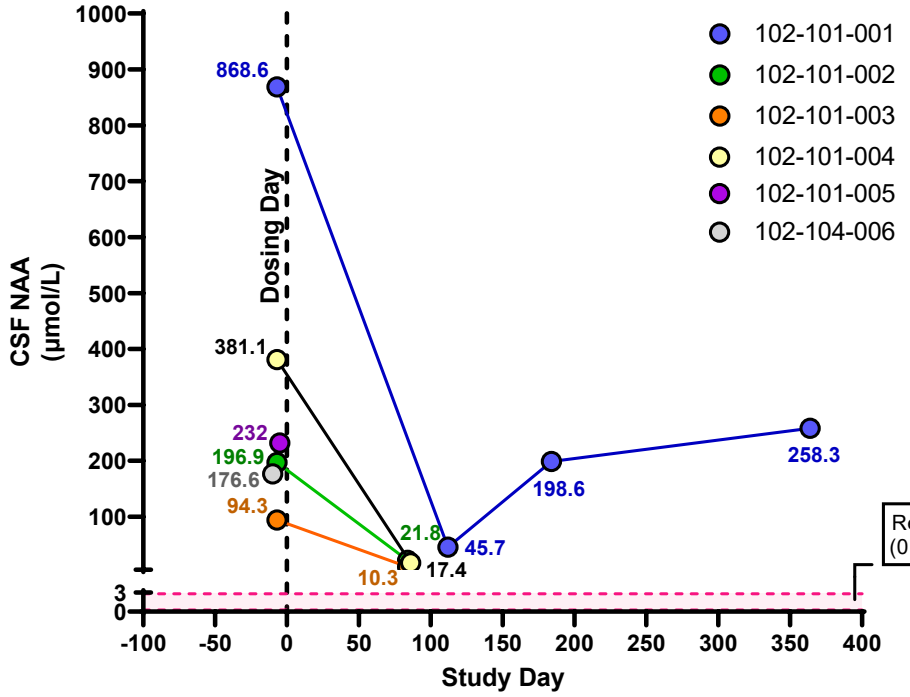
Rapid and Persistent Decrease in Urine NAA Seen in All Participants Post-BBP-812



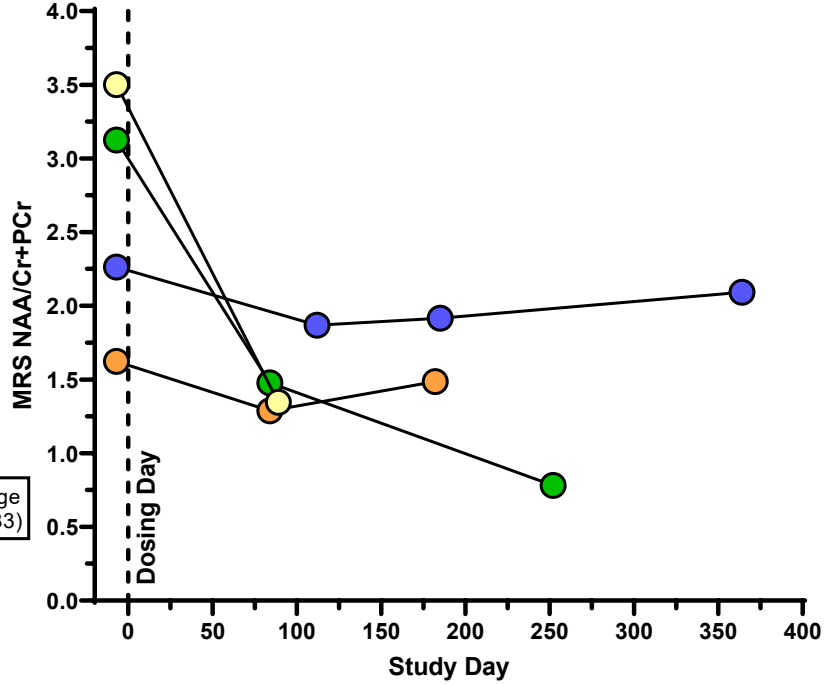
Aspa
a bridgebio company

Decreased NAA in Cerebrospinal Fluid and Brain MRS Seen in All Participants Post-BBP-812

CSF



Right Frontal White Matter by MRS

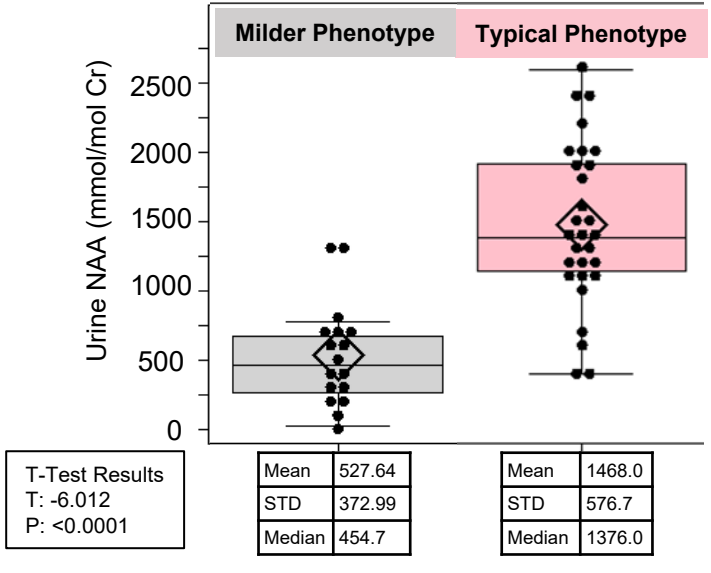


Lower NAA Levels are Associated with Milder Disease

NAA from Natural History

- Data from CVN-101 natural history study, CVN-102 baseline and literature review
- Mild phenotype defined as ability to pull to stand
  - ~10% of CVN-101 population

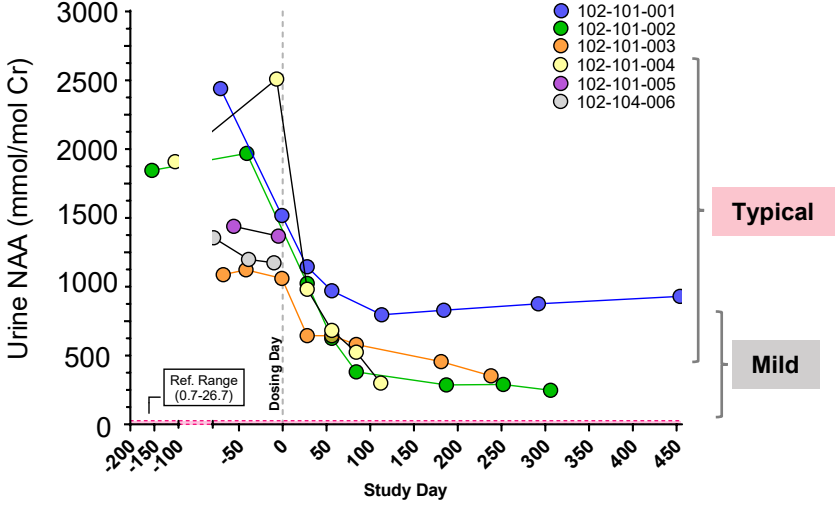
Average urine NAA lower in mild vs. typical phenotype



NAA Pre- and Post-BBP-812 Treatment

- Pre-treatment: all NAA levels in typical range for Canavan disease

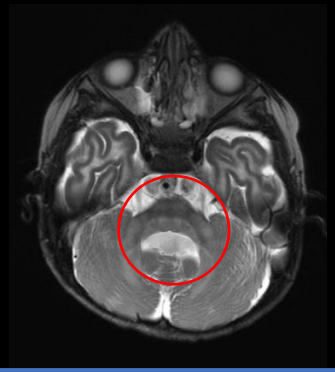
Post-treatment: NAA levels fell to mild range



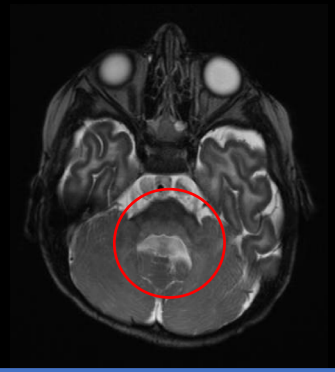
Myelination in Brainstem and Cerebellar Peduncles Pre and Post Intravenous AAV9-h*ASPA* (BBP-812)

001

Baseline: 29 mo

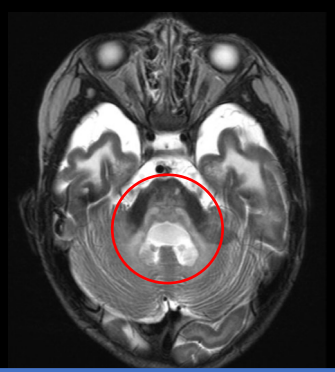


12 months post-tx: 41 mo

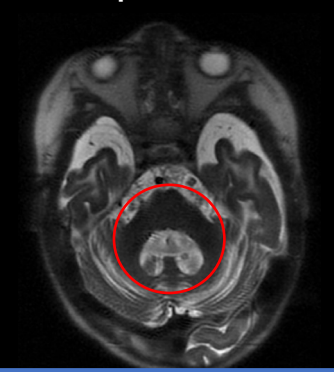


002

Baseline: 19 mo

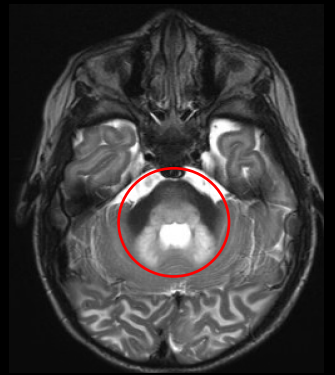


9 mo post-tx: 28 mo

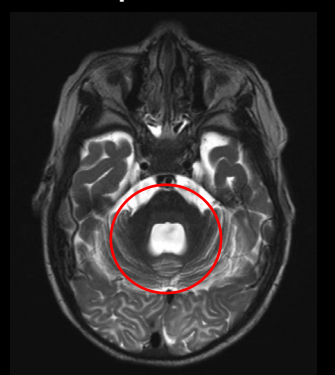


003

Baseline: 22 mo

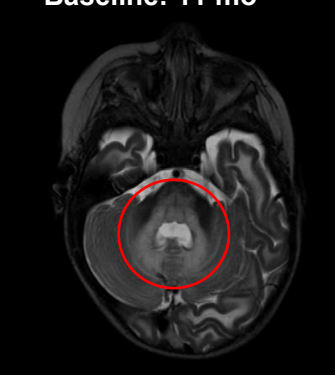


6 mo post-tx: 28 mo

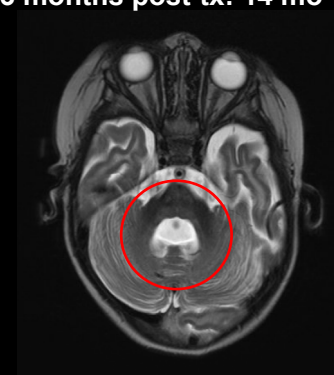


004

Baseline: 11 mo



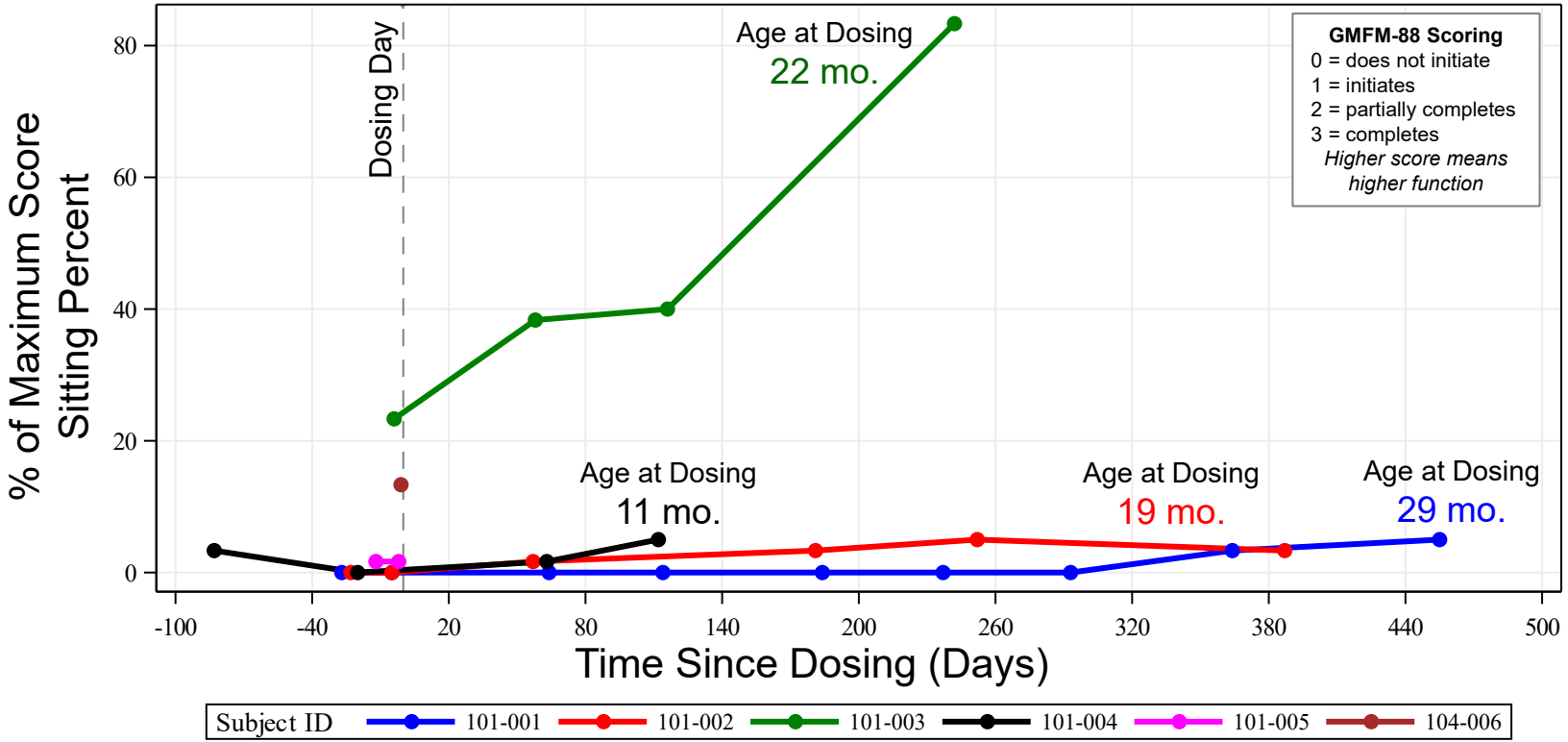
3 months post-tx: 14 mo



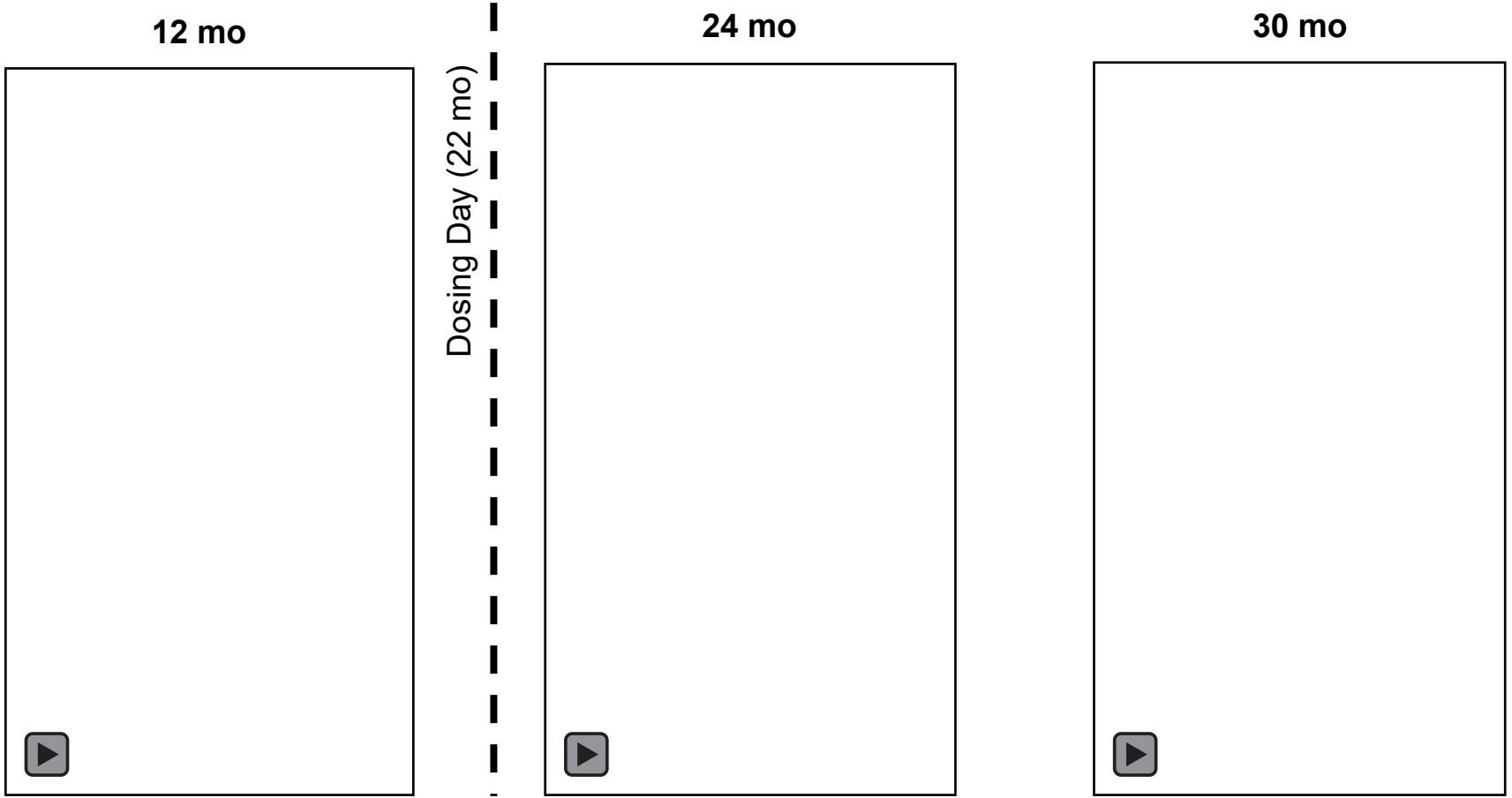
All images are T2 MRI sequences obtained on 3T scanner

CVN-102: Improvement in GMFM-88 Sitting Dimension After BBP-812 Treatment

GMFM-88 Sitting Dimension Assesses both Sitting Ability and Upright Head Control



Changes Observed After Intravenous AAV9-*ASPA* (BBP-812) in One CVN-102 Study Participant



BBP-812 Safety Summary

- Data cut-off 25 Mar 2023
- Total of 6 participants dosed at 1.32x10^14 vg/kg
- Exposure duration: <1 mo – 17 mo
- 5 treatment-emergent serious adverse events reported in 3 participants

Preferred Term	**Relatedness to BBP-812**	**Severity**	**Outcome**
Subdural haemorrhage	Unlikely	Severe	Not recovered / Not resolved
Seizure	Unlikely	Severe	Recovered / Resolved
Gastrostomy	Not related	Severe	Recovered / Resolved
Vomiting	Unlikely	Severe	Not recovered / Not resolved
Decerebrate posture	Possibly	Moderate	Recovered / Resolved

Summary

- CVN-101 natural history:
  - Robust comparison group for CVN-102
  - Persistent and profound motor performance deficits in children with Canavan disease
    - Vast majority of children function at or below the 6-month level
- Pharmacodynamics of BBP-812:
  - Rapid and marked **decreases in NAA** across all compartments tested (brain-MRS, CSF and urine) consistent with expression of active ASPA enzyme
- Safety of BBP-812:
  - BBP-812 at 1.32E14 vg/kg generally **well-tolerated**
    - 4/5 treatment-emergent SAEs considered not or unlikely related to BBP-812 (1 possibly related)
    - Laboratory findings have been expected and **manageable**
- Clinical efficacy of BBP-812:
  - Preliminary data on imaging and motor function show encouraging changes
  - **More data and longer follow-up are needed to fully characterize potential clinical benefit**